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Original Contribution

Pancreatic Cancer and Exposure to Dietary Nitrate and Nitrite in the NIH-AARP Diet and Health Study

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Nitrate and nitrite are precursors of *N*-nitroso compounds, which induce tumors of the pancreas in animals. The authors evaluated the relation of dietary nitrate and nitrite to pancreatic cancer risk in the NIH-AARP Diet and Health Study. Nitrate and nitrite intakes were assessed at baseline using a 124-item food frequency questionnaire. During approximately 10 years of follow-up between 1995 and 2006, 1,728 incident pancreatic cancer cases were identified. There was no association between total nitrate or nitrite intake and pancreatic cancer in men or women. However, men in the highest quintile of summed nitrate/nitrite intake from processed meat had a nonsignificantly elevated risk of pancreatic cancer (hazard ratio = 1.18, 95% confidence interval: 0.95, 1.47; *P*-trend = 0.11). The authors observed a stronger increase in risk among men for nitrate/nitrite intake from processed meat at ages 12–13 years (highest quintile vs. lowest: hazard ratio = 1.32, 95% confidence interval: 0.99, 1.76; *P*-trend = 0.11), though the relation did not achieve statistical significance. The authors found no associations between adult or adolescent nitrate or nitrite intake from processed meats and pancreatic cancer among women. These results provide modest evidence that processed meat sources of dietary nitrate and nitrite may be associated with pancreatic cancer among men and provide no support for the hypothesis in women.

diet; nitrates; nitrites; nitroso compounds; pancreatic neoplasms

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health; NOCs, *N*-nitroso compounds; SD, standard deviation.

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States, accounting for approximately 5% of all cancer deaths (1). Although smoking, obesity, and a history of diabetes are most consistently associated with increased risk of pancreatic cancer, the etiology of this malignancy is poorly understood (2). Various dietary factors have been investigated in relation to pancreatic cancer (2–9). The role of dietary nitrate and nitrite is of interest, as they are precursors of *N*-nitroso compounds (NOCs), which induce pancreatic tumors in animals (10, 11) and potentially in humans (12).

Nitrite and nitrate salts are added to cured meats, such as bacon, hot dogs, and ham, to prevent the growth of spore-forming bacteria, as well as to add color and flavor (11, 13). Nitrate is a natural component of plants and is found at high concentrations in leafy vegetables, such as lettuce and spinach, and some root vegetables, such as beets (14). Ingested nitrate is absorbed in the small intestine, and 25% is excreted in the mouth, where oral bacteria reduce it to nitrite (15). In the acidic stomach, nitrite forms nitrous acid, which decomposes into various reactive nitrogen species. Nitrite and reactive nitrogen species react with nitrosatable compounds, mainly amines and amides, to form NOCs (15–17). It is hypothesized that risk of pancreatic cancer is increased by long-term exposure of pancreatic ductular epithelium to NOCs through the circulation, where metabolic activation can occur if it has not already occurred in the liver (18, 19). Metabolically activated NOCs induce DNA adducts and

single strand breaks and may stimulate DNA synthesis in the pancreatic ductular epithelium (20, 21). Chronic NOC exposure is subsequently hypothesized to induce tumor development by affecting DNA repair capabilities (22).

In a case-control study of 189 pancreatic cancer cases in Iowa, Coss et al. (23) observed a positive association between dietary nitrite from animal sources and pancreatic cancer (odds ratio = 2.3, 95% confidence interval (CI): 1.1, 5.1). Although some investigators have reported no association between intake of smoked or processed meat (8, 24) or nitrite (25, 26) and pancreatic cancer, others have found increased risks (7, 9, 27, 28) or statistically significant trends in increasing risk (29–33). Intake of vitamin C, which inhibits *N*-nitrosation, has been inversely associated with pancreatic cancer in most studies (25, 27, 30, 34–36), although not consistently (37). Most of these studies have found positive associations with meat or cholesterol and inverse associations with fruit and vegetable consumption for pancreatic cancer, and the degree to which the associations with NOC-related exposures are attenuated by vitamin C intake is not clear, since it has not been evaluated previously.

Most of the investigations conducted to date have been case-control studies, which are subject to dietary recall bias and the use of proxy interviews because of the high fatality rate of pancreatic cancer. Most prospective studies have had too few cases and thus inadequate statistical power. Previously in this study population, Stolzenberg-Solomon et al. (6) found that total meat intake, intake of red meat, and intake of meat cooked at high temperatures were positively associated with pancreatic cancer among men, but no association was observed for processed meats. In this project, we extended these findings by evaluating the role that nitrate and nitrite components of meat and other foods may play in pancreatic cancer development. Here we present results for prospectively collected data from the National Institutes of Health (NIH)-AARP Diet and Health Study on the relation between adult and adolescent nitrate and nitrite intake from food sources, as potential precursors of NOCs, and the risk of pancreatic cancer.

MATERIALS AND METHODS

Study population

The NIH-AARP Diet and Health Study was initiated in 1995 when a baseline questionnaire was mailed to AARP members aged 50–71 years residing in one of 6 US states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or 2 US metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) (37). This questionnaire ascertained information on usual dietary and supplement intake over the past 12 months, as well as on other risk factors and demographic characteristics. Approximately 6 months later, participants were mailed a risk factor questionnaire which elicited detailed information on meat intake. An abbreviated food frequency questionnaire assessed intake of 37 selected food items at ages 12–13 years. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

After excluding duplicates and participants who died or moved before study entry or withdrew from the study, a total of 566,402 participants returned the baseline questionnaire and 332,913 completed the risk factor questionnaire. For the analyses of baseline data, we excluded persons whose questionnaire had been filled in by someone else on their behalf ($n = 15{,}760$), those who had been previously diagnosed with cancer, except for nonmelanoma skin cancer ($n = 51{,}234$), those with extreme values for total energy intake (beyond twice the interquartile range of Box-Cox log-transformed intake; $n = 4{,}417$), and those without residential data ($n = 2{,}765$). After these exclusions, 492,226 participants (293,491 men and 198,735 women) were available for analysis. After all exclusions, the risk factor questionnaire cohort consisted of 303,156 persons (176,842 men and 126,314 women).

Cancer ascertainment

Incident cases of first primary pancreatic cancer (*International Classification of Diseases for Oncology*, Third Edition (38), code C25) were identified through December 31, 2006, via linkage of the cohort database to the cancer registries of the 8 original states plus 2 additional states (Texas and Arizona) and the National Death Index Plus. The state cancer registries are certified by the North American Association of Central Cancer Registries as meeting the highest standard of quality. In a validation study, 90% of cancer cases in our cohort were validly identified via linkage to state cancer registries (39). During an average of 10 years of follow-up, 1,728 incident pancreatic cancer cases were identified (1,103 men, 625 women); of these, 1,055 persons (658 men, 397 women) completed the risk factor questionnaire.

Dietary intake

The dietary component of the baseline questionnaire asked about the frequency of consumption and corresponding portion sizes of 124 food items, including 14 fruits and 23 vegetables, and fresh and processed meats during the past 12 months. Participants were queried about their frequency of intake in 10 categories ranging from ''never'' to ''2+ times per day'' for foods and ''never'' to ''6+ times per day'' for beverages. Each line item was accompanied by 3 possible portion size categories. The food items, portion sizes, nutrient database, and Pyramid Food Servings Database were used in conjunction with national dietary data from the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals (40, 41). The Pyramid Food Servings Database utilized a recipe file to disaggregate food mixtures into their component ingredients and assign them to food groups. The food frequency questionnaire was validated using two 24-hour recalls in a subset of the cohort (42).

The risk factor questionnaire queried about adolescent intake (at ages 12–13 years) of processed meats (bacon or sausage; hot dogs or frankfurters; and cold cuts or luncheon meats, such as ham, bologna, salami, corned beef, or pastrami), as well as major sources of vitamin C (e.g., citrus fruits, fruit juice, tomatoes, and broccoli). Sex- and age-specific portion

sizes were estimated from national dietary data from the 1965–1966 Household Food Consumption Survey (43), the survey performed closest to the calendar time when cohort members were aged 12–13 years.

We determined the nitrate and nitrite contents of the foods on the questionnaires from the literature, as described previously (44, 45). Nitrate values ranged from 0 to 180.0 mg/100 g, with the highest concentrations occurring in vegetable products. Nitrite values ranged from 0 to 7.17 mg/100 g, with the highest concentrations occurring in meat. Daily intakes of nitrate and nitrite were calculated by multiplying the frequency of consumption of each food by the nitrate or nitrite content of the food and summing across all food items. Intakes were computed separately for animal and plant sources. We also evaluated intake of nitrate and nitrite from processed meats, which included both red- and white-meat sources of bacon, sausage, luncheon meats, cold cuts, ham, and hot dogs. Furthermore, for adult intake estimated from the baseline questionnaire, we also estimated intakes of nitrate and nitrite from processed meats using a database of measured levels in processed meats purchased in 2004, which represent 90% of processed meats consumed in the United States; NOCs were undetectable in these samples (46, 47).

For men, the major contributors to nitrate intake were lettuce (33.8%), cooked spinach/greens (9.8%), and broccoli (4.1%), and the major contributors to nitrite intake were cold cuts (8.6%), breads/rolls (7.1%), and pasta (6.6%). Among women, the major contributors to nitrate intake were also lettuce (35.2%), cooked spinach/greens (10.7%), and broccoli (5.2%), whereas the major contributors to nitrite intake were pasta (6.8%), rice/grains (6.5%), and breakfast cereals (6.4%). In our study population, the correlation between intake at baseline and intake at ages 12–13 years was 0.30 for nitrate and 0.29 for nitrite.

The usual source of drinking water and tap water intake was not assessed for the cohort; therefore, we used the census tract location of a participant's residence at enrollment to estimate the likelihood that the participant may have been exposed to elevated nitrate concentrations via the drinking water supply, as previously described (46). We calculated the area within each census tract that intersected grid cells with estimated nitrate concentrations greater than or equal to 10 mg/L. In sensitivity analyses, we excluded participants who resided in census tracts where at least 50% of the area was predicted to have nitrate levels greater than or equal to 10 mg/L, because their nitrate intake from water sources might have exceeded that from their diet ($n = 11{,}801$ study participants (39 pancreatic cancer cases); 2.4% of the study population).

Statistical analysis

Person-years of follow-up for each participant accrued from the date of return of the baseline questionnaire to the date of pancreatic cancer diagnosis, the date of moving out of the registry ascertainment area, death, or the end of the follow-up period (December 31, 2006). Cox proportional hazards regression models with person-years as the underlying time metric were used to estimate hazard ratios and 95% confidence intervals for pancreatic cancer according to quintiles of nitrate and nitrite intake. Tests for linear trend were conducted using the median value of each exposure category as a continuous variable in the model. The proportional hazards assumption was tested and upheld in all analyses. In all multivariate models, hazard ratios were adjusted for age, energy intake (continuous), smoking status (never, current, or former smoker), race (white, black, or other), family history of any cancer (yes, no), body mass index (weight (kg)/height $(m)^2$; <25, 25–29.9, 30–34.9, or ≥ 35), history of diabetes (yes, no), and dietary intakes of vitamin C (mg/day), saturated fat (g/day), and folate (g/day). We evaluated a more detailed (31-level) smoking variable; however, it did not produce a substantial alteration in the results when compared with the simpler (never, current, or former) smoking variable. We also evaluated the roles of heterocyclic amines and temperature as confounders in the subpopulation of persons who completed the risk factor questionnaire. Nitrate and nitrite intakes (mg/day) were adjusted for energy intake using the nutrient density method (47), which expresses intake per 1,000 calories.

We stratified results by factors potentially affecting *N*-nitrosation, and to evaluate the consistency of the associations, we stratified results by potential risk factors. We assessed multiplicative interactions by adding the relevant cross-product term to the main-effects models in sex-specific analyses. We repeated our analyses in a sample restricted to persons without a potentially high intake of nitrate from drinking water. For all comparisons, *P* values were 2-sided, and $\alpha < 0.05$ indicated statistical significance.

RESULTS

The mean dietary nitrate intake in the cohort was 88 mg/day (standard deviation (SD), 65), and the mean nitrite intake was 1.2 mg/day (SD, 0.6). The average of the combined nitrate and nitrite intakes from processed meat sources was 1.3 mg/day (SD, 1.5) (1.6 mg/day (SD, 1.8) among men and 0.8 mg/day (SD, 1.0) among women). Men consumed more processed, red, and white meat than did women.

Compared with those in the lowest quintile, men (Table 1) and women (Table 2) in the highest quintile of nitrate intake were more educated, more physically active, and more likely to consume fruits and vegetables, but they consumed fewer calories. Men and women in the highest quintile of nitrite intake tended to be more educated, more physically active, and more likely to consume fruits, vegetables, and processed meats, but they were less likely to be white and less likely to be current or former smokers than those in the lowest nitrite intake quintile.

We did not observe any associations between total nitrate or nitrite intake and pancreatic cancer in men or women (Table 3); furthermore, when we examined nitrite intake from plant and animal sources separately, there were no significant associations. For men and women combined, intake of nitrate and nitrite from processed meats consumed within the past year, intake during adolescence, and past-year intake calculated using measured processed meat values were not associated with pancreatic cancer (Table 4).

Table 1. Baseline Characteristics of Male Participants ($n = 293{,}491$) in the NIH-AARP Diet and Health Study, by Quintiles of Nitrate and Nitrite Intake, 1995–2006

Characteristic	Nitrate										Nitrite									
	Q1 (19.3 and 34.8)[a]		Q2 (29.9 and 56.9)		Q3 (40.9 and 75.0)		Q4 (57.4 and 95.3)		Q5 (94.8 and 150.3)		Q1 (0.5 and 0.8)		Q2 (0.6 and 1.0)		Q3 (0.7 and 1.2)		Q4 (0.7 and 1.2)		Q5 (0.9 and 1.6)	
	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean
Age, years		61.7		62.1		62.3		62.3		62.4		61.6		62.0		62.2		62.4		62.6
Race																				
Non-Hispanic white	91.8		93.1		93.1		92.7		91.6		93.5		94.2		93.7		92.5		88.1	
Non-Hispanic black	3.2		2.6		2.4		2.6		2.6		3.1		2.5		2.5		2.5		3.0	
Hispanic, Asian, Pacific Islander, American Indian, Alaska Native, or unknown	5.0		4.3		4.5		4.8		5.9		3.4		3.4		3.8		5.0		9.0	
Positive family history of cancer	46.8		47.2		47.0		47.2		46.3		47.1		47.5		47.4		47.1		45.5	
Currently married	81.3		85.8		86.7		86.1		85.6		81.5		86.0		86.5		86.6		84.7	
Body mass index[b]		27.3		27.4		27.3		27.3		27.0		27.2		27.4		27.4		27.3		27.0
Smoking history																				
Never smoker	25.5		29.5		30.8		30.7		31.2		23.7		29.2		30.4		31.5		32.3	
Former smoker	53.4		56.2		57.2		58.3		59.3		55.8		56.3		56.7		56.9		57.0	
Current smoker or quit <1 year previously	17.1		10.5		8.0		7.1		5.5		16.5		10.8		9.2		7.9		6.4	
College graduate or postgraduate education	34.9		43.3		47.4		49.9		52.9		41.9		45.4		45.5		45.4		44.8	
Vigorous physical activity, >5 times per week	16.5		19.2		21.7		24.4		28.6		18.5		19.6		20.7		22.4		26.1	
Dietary intake																				
Energy, kcal/day		2,202		2,037		1,974		1,955		1,776		2,249		2,032		1,987		1,933		1,826
Vegetables, servings/1,000 kcal		2.5		3.4		4.1		4.9		6.3		3.4		3.8		4.0		4.2		4.7
Fruit, servings/1,000 kcal		2.3		2.8		3.1		3.4		3.7		2.7		2.8		3.0		3.1		3.4
Processed meat, g/1,000 kcal		13.2		12.9		12.0		11.0		9.4		8.1		10.5		11.9		13.5		16.6
Vitamin C, mg/1,000 kcal		61.4		76.9		87.3		97.8		118.2		76.2		81.5		84.2		87.5		96.0
Vitamin E, mg/1,000 kcal		4.2		4.7		4.9		5.1		5.7		4.3		4.9		5.0		5.0		5.0

Abbreviations: NIH, National Institutes of Health; Q, quintile.

[a] Energy-adjusted quintile median (mg/1,000 kcal) and unadjusted quintile median (mg/day), respectively, for the entire cohort (both men and women).

[b] Weight (kg)/height $(m)^2$.

Table 2. Baseline Characteristics of Female Participants ($n = 198,735$) in the NIH-AARP Diet and Health Study, by Quintiles of Nitrate and Nitrite Intake, 1995–2006

Characteristic	Nitrate										Nitrite									
	Q1 (19.3 and 34.8)[a]		Q2 (29.9 and 56.9)		Q3 (40.9 and 75.0)		Q4 (57.4 and 95.3)		Q5 (94.8 and 150.3)		Q1 (0.5 and 0.8)		Q2 (0.6 and 1.0)		Q3 (0.7 and 1.2)		Q4 (0.7 and 1.2)		Q5 (0.9 and 1.6)	
	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean
Age, years		61.5		61.8		61.9		62.0		61.8		61.4		61.8		61.9		62.0		62.1
Race																				
Non-Hispanic white	88.1		89.6		90.3		89.5		89.0		89.2		91.1		90.6		90.1		86.3	
Non-Hispanic black	6.4		5.7		5.4		5.5		5.5		7.2		5.3		5.3		5.1		5.5	
Hispanic, Asian, Pacific Islander, American Indian, Alaska Native, or unknown	5.5		4.7		4.4		5.0		5.5		3.6		3.6		4.1		4.8		8.2	
Positive family history of cancer	50.5		51.4		51.5		51.2		50.9		50.9		50.9		51.9		51.5		50.4	
Currently married	38.1		43.1		45.6		46.2		45.4		40.7		45.0		46.3		46.3		43.0	
Body mass index[b]		27.2		27.1		27.0		26.9		26.5		26.7		26.9		27.0		27.0		26.6
Smoking history																				
Never smoker	42.1		45.3		46.1		45.0		42.1		36.1		42.8		45.1		46.9		47.7	
Former smoker	30.5		35.2		36.9		39.6		43.3		35.7		37.4		38.6		39.2		39.8	
Current smoker or quit <1 year previously	23.6		16.3		13.6		12.0		10.7		14.5		16.4		13.0		10.5		8.4	
College graduate or postgraduate education	20.1		25.6		29.0		32.1		35.1		25.1		27.9		30.0		31.0		33.9	
Vigorous physical activity, >5 times per week	10.5		12.3		14.3		16.6		21.7		12.4		14.1		14.9		16.8		21.3	
Dietary intake																				
Energy, kcal/day		1,701		1,623		1,602		1,572		1,461		1,663		1,608		1,591		1,559		1,461
Vegetables, servings/ 1,000 kcal		1.9		2.7		3.3		4.0		5.6		2.9		3.4		3.7		4.0		4.8
Fruit, servings/ 1,000 kcal		2.1		2.5		2.9		3.2		3.5		2.7		2.8		2.9		3.1		3.3
Processed meat, g/1,000 kcal		9.7		9.5		8.8		8.1		6.7		6.3		7.7		8.4		9.0		9.5
Vitamin C, mg/1,000 kcal		68.0		82.2		93.5		105.9		129.7		91.6		93.2		97.6		102.8		119.3
Vitamin E, mg/1,000 kcal		4.4		4.8		5.0		5.3		5.9		4.7		5.2		5.2		5.3		5.5

Abbreviations: NIH, National Institutes of Health; Q, quintile.

[a] Energy-adjusted quintile median (mg/1,000 kcal) and unadjusted quintile median (mg/day), respectively, for the entire cohort (both men and women).

[b] Weight (kg)/height $(m)^2$.

Table 3. Multivariate Hazard Ratios[a] for Pancreatic Cancer According to Quintile of Nitrate or Nitrite Intake in the NIH-AARP Diet and Health Study, 1995–2006

Quintile	Median Value, mg/1,000 kcal	Total (n = 1,728)			Men (n = 1,103)			Women (n = 628)		
		No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Nitrate										
Quintile 1	19.3	370	1.00	Reference	282	1.00	Reference	88	1.00	Reference
Quintile 2	29.9	330	0.91	0.78, 1.06	229	0.91	0.76, 1.09	101	0.89	0.67, 1.19
Quintile 3	40.9	360	1.02	0.88, 1.18	232	1.05	0.88, 1.25	128	0.93	0.71, 1.23
Quintile 4	57.4	340	0.99	0.85, 1.16	204	1.07	0.89, 1.30	136	0.84	0.64, 1.11
Quintile 5	94.8	322	1.01	0.85, 1.20	151	1.07	0.86, 1.33	171	0.88	0.66, 1.17
P for trend			0.58			0.27			0.49	
Nitrite										
Quintile 1	0.45	361	1.00	Reference	238	1.00	Reference	123	1.00	Reference
Quintile 2	0.57	361	0.99	0.86, 1.16	236	1.03	0.86, 1.24	125	0.93	0.72, 1.19
Quintile 3	0.65	331	0.92	0.79, 1.08	220	1.00	0.82, 1.21	111	0.78	0.60, 1.02
Quintile 4	0.74	348	0.97	0.83, 1.14	210	0.99	0.81, 1.20	138	0.92	0.72, 1.19
Quintile 5	0.9	321	0.92	0.78, 1.08	194	0.97	0.79, 1.20	127	0.81	0.61, 1.06
P for trend			0.31			0.67			0.18	
Plant sources of nitrite										
Quintile 1	0.25	380	1.00	Reference	285	1.00	Reference	95	1.00	
Quintile 2	0.34	380	1.02	0.88, 1.18	253	0.98	0.82, 1.16	127	1.12	0.86, 1.47
Quintile 3	0.42	315	0.87	0.74, 1.01	199	0.85	0.70, 1.03	116	0.91	0.69, 1.21
Quintile 4	0.51	350	0.99	0.84, 1.16	199	0.95	0.78, 1.17	151	1.06	0.80, 1.39
Quintile 5	0.68	303	0.91	0.76, 1.09	167	0.94	0.75, 1.18	136	0.89	0.65, 1.20
P for trend			0.32			0.61			0.29	
Animal sources of nitrite										
Quintile 1	0.1	300	1.00	Reference	157	1.00	Reference	143	1.00	Reference
Quintile 2	0.15	340	1.07	0.92, 1.25	209	1.16	0.94, 1.44	131	0.97	0.76, 1.23
Quintile 3	0.2	363	1.11	0.95, 1.30	229	1.16	0.94, 1.43	134	1.06	0.83, 1.34
Quintile 4	0.25	378	1.11	0.95, 1.30	260	1.21	0.98, 1.48	118	0.99	0.77, 1.27
Quintile 5	0.36	347	0.96	0.82, 1.13	248	0.99	0.80, 1.23	99	0.94	0.72, 1.22
P for trend			0.41			0.41			0.69	

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, other, or missing), total energy intake (continuous), smoking status, family history of cancer, family history of diabetes, body mass index (weight (kg)/height (m)^2; <25, 25–29.9, 30–34.9, or ≥35), and intakes of saturated fat, folate, and vitamin C.

However, among men, the hazard ratio for pancreatic cancer was elevated in the highest (vs. lowest) quintile of combined nitrate and nitrite intake from processed meat sources in the past year (hazard ratio (HR) = 1.18, 95% CI: 0.95, 1.47; Table 4), although the *P* value for trend was not statistically significant (*P*-trend = 0.11). No positive associations were observed among women. The interaction between nitrate and nitrite intake from processed meat and gender was not significant (*P*-interaction = 0.10). Compared with the first quintile, the hazard ratios for pancreatic cancer were elevated across all other quintiles of nitrate and nitrite intake during adolescence in men (quintile 2: HR = 1.39, 95% CI: 1.10, 1.76; quintile 3: HR = 1.25, 95% CI: 0.97, 1.60; quintile 4: HR = 1.46, 95% CI: 1.13, 1.87; quintile 5: HR = 1.32, 95% CI: 0.99, 1.76) (Table 4). The analysis of measured nitrate and nitrite values from processed meats was consistent with these results (Table 4).

Because vitamins C and E and red meat intake affect endogenous formation of NOCs, we conducted analyses stratified by the median adult intake of each of these dietary factors. Men in the highest quintile of nitrate and nitrite from processed meat who also had a low vitamin C intake had a higher risk of pancreatic cancer than those with a higher vitamin C intake, although these associations were not statistically significant (HR = 1.29 (95% CI: 0.92, 1.80) and HR = 1.12 (95% CI: 0.83, 1.51), respectively) (Table 5); furthermore, none of the tested interactions were statistically significant. We also stratified our analyses by age (median), education (no college/some college), body mass index (above/below the median), and physical activity (above/

Table 4. Multivariate Hazard Ratios[a] for Pancreatic Cancer According to Quintile of Nitrate Plus Nitrite Intake From Processed Meat Sources in the NIH-AARP Diet and Health Study, 1995–2006

Quintile	Median Value, mg/1,000 kcal	Total			Men			Women		
		No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Intake from processed meats in the past year										
Quintile 1	0.11	297	1.00	Reference	135	1.00	Reference	162	1.00	Reference
Quintile 2	0.29	335	1.06	0.91, 1.25	176	1.05	0.84, 1.32	159	1.11	0.89, 1.38
Quintile 3	0.49	343	1.05	0.90, 1.24	211	1.08	0.87, 1.35	132	1.06	0.84, 1.35
Quintile 4	0.77	356	1.05	0.90, 1.24	266	1.18	0.95, 1.47	90	0.87	0.67, 1.14
Quintile 5	1.43	391	1.09	0.93, 1.29	310	1.18	0.95, 1.47	81	0.97	0.73, 1.28
P for trend			0.40			0.11			0.38	
Intake from processed meats at ages 12–13 years										
Quintile 1	0.21	198	1.00	Reference	126	1.00	Reference	111	1.00	Reference
Quintile 2	0.65	233	1.16	0.96, 1.41	162	1.39	1.10, 1.76	94	1.01	0.77, 1.33
Quintile 3	1.19	204	1.09	0.89, 1.32	132	1.25	0.97, 1.60	70	0.89	0.66, 1.20
Quintile 4	1.91	219	1.18	0.97, 1.44	139	1.46	1.13, 1.87	69	1.06	0.78, 1.44
Quintile 5	3.33	201	1.11	0.91, 1.36	99	1.32	0.99, 1.76	53	0.94	0.67, 1.32
P for trend			0.46			0.11			0.83	
Intake based on measured values in processed meats										
Quintile 1	0.04	300	1.00	Reference	136	1.00	Reference	164	1.00	Reference
Quintile 2	0.10	360	1.13	0.97, 1.32	185	1.08	0.86, 1.35	175	1.23	0.99, 1.52
Quintile 3	0.18	328	1.00	0.85, 1.18	211	1.05	0.84, 1.31	117	0.93	0.76, 1.24
Quintile 4	0.28	364	1.07	0.91, 1.26	271	1.16	0.94, 1.44	93	0.90	0.72, 1.21
Quintile 5	0.48	376	1.05	0.89, 1.23	300	1,13	0.91, 1.41	76	1.09	0.68, 1.20
P for trend			0.96			0.26			0.63	

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, other, or missing), total energy intake (continuous), smoking status, family history of cancer, family history of diabetes, body mass index (weight (kg)/height (m)^2; <25, 25–29.9, 30–34.9, or ≥ 35), and intakes of saturated fat, folate, and vitamin C.

below 3–4 times per week); results were similar by levels of these factors for men and women. We evaluated the roles of heterocyclic amines and temperature as confounders among persons who completed the risk factor questionnaire, though no difference in risk was observed with inclusion of these variables in the models. Our results were unchanged when we excluded the 2.4% of the study population (39 pancreatic cancer cases) who resided in census tracts with predicted high levels of nitrate in water supplies.

DISCUSSION

In this large, prospective cohort study, dietary intake of nitrate and nitrite from processed meats during adulthood and adolescence was positively associated with pancreatic cancer in men, though the relation did not achieve statistical significance. Total nitrate and nitrite intake was not associated with pancreatic cancer in men or women.

Dietary nitrite from animal sources was positively associated with pancreatic cancer (odds ratio = 2.3, 95% CI: 1.1, 5.1) in a population-based case-control study in Iowa (23). A few other studies evaluated dietary intake of nitrate and nitrite and pancreatic cancer, although they did not evaluate plant and animal sources separately. In a case-control study, Howe et al. (25) found no association between dietary nitrate and nitrite and pancreatic cancer, whereas in another case-control study, Baghurst et al. (26) reported an inverse association between dietary nitrate and pancreatic cancer but no association for dietary nitrite. Previous studies have found elevated risks of pancreatic cancer with increased consumption of smoked or processed meats (9, 16). In the Multiethnic Cohort Study, persons in the fifth quintile of processed meat intake had an elevated risk of pancreatic cancer compared with those in the lowest quintile (relative risk = 1.68, 95% CI: 1.35, 2.07; *P*-trend < 0.01) (9). Intake of processed meat, specifically bacon and smoked ham, was associated with increased risk of pancreatic cancer in

Table 5. Multivariate Hazard Ratios[a] for Pancreatic Cancer According to Quintile of Nitrate Plus Nitrite Intake From Processed Meat Sources, by Level of Vitamin C Intake, in the NIH-AARP Diet and Health Study, 1995–2006

Quintile	Median Value, mg/1,000 kcal	Total			Men			Women		
		No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Low vitamin C intake										
Quintile 1	0.15	111	1.00	Reference	47	1.00	Reference	64	1.00	Reference
Quintile 2	0.44	157	1.09	0.86, 1.40	75	1.04	0.72, 1.51	82	1.18	0.85, 1.64
Quintile 3	0.81	178	1.12	0.88, 1.43	105	1.17	0.83, 1.66	73	1.12	0.80, 1.58
Quintile 4	1.40	192	1.10	0.86, 1.40	146	1.31	0.94, 1.84	46	0.81	0.55, 1.19
Quintile 5	2.90	236	1.17	0.92, 1.49	184	1.29	0.92, 1.80	52	1.05	0.71, 1.53
P for trend			0.28			0.09			0.60	
High vitamin C intake										
Quintile 1	0.21	186	1.00	Reference	88	1.00	Reference	98	1.00	Reference
Quintile 2	0.65	179	1.06	0.86, 1.30	102	1.09	0.82, 1.46	77	1.04	0.77, 1.41
Quintile 3	1.19	167	1.02	0.82, 1.27	108	1.06	0.79, 1.41	59	1.01	0.72, 1.40
Quintile 4	1.91	165	1.04	0.83, 1.30	121	1.10	0.82, 1.48	44	0.95	0.66, 1.38
Quintile 5	3.33	157	1.04	0.82, 1.32	127	1.12	0.83, 1.51	30	0.90	0.58, 1.38
P for trend			0.86			0.53			0.53	
P for interaction			0.51			0.55			0.79	

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, other, or missing), total energy intake (continuous), smoking status, family history of cancer, family history of diabetes, body mass index (weight (kg)/height $(m)^2$; <25, $25-29.9$, $30-34.9$, or ≥ 35), and intakes of saturated fat and folate.

a case-control study in Sweden (29). However, in a US case-control study carried out in Atlanta, Detroit, and 10 New Jersey counties, no significant change in risk was observed with increasing red or processed meat intake in either men or women (8). Similarly, in a case-control study in Los Angeles County, Mack et al. (27) did not find an association between processed meat intake and pancreatic cancer in either men or women.

There can be substantial interindividual variability in the production of NOCs, which is mediated by several known factors. Animal products containing nitrite (primarily processed meats) are a source of amines and amides, which are also precursors of NOCs. As a result, consumption of nitrite from animal products should result in more substantial exposure to NOCs than consumption from plant-based products. Furthermore, a number of preformed NOCs are found in processed meats (48, 49), although we did not detect NOCs in processed meats measured in 2004. Nitrate is derived almost entirely from vegetables, which also contain inhibitors of in vivo *N*-nitrosation, which may partly explain their consistent inverse associations with many epithelial cancers (12, 28). Further, nitrate and nitrite consumed in vegetable products are not likely to result in significant formation of NOCs (50). Our results modestly suggest that *N*-nitrosation inhibition by vitamin C in pancreatic cancer etiology may be important to consider, although we did not observe a significant interaction. Concomitant consumption of nitrite and vitamin C is likely to be most important for inhibition of endogenous nitrosation (50), but we were not able to assess this using our questionnaire.

We compared our estimates from the literature (mostly reflecting levels in the 1970s) with our estimates from laboratory measurements of processed meats conducted in 2004 and found that the nitrite concentrations had decreased in comparison with previous decades. Likewise, nitrate levels based on published values were at least 5 times higher than measured values for hot dogs and other sausages, ham steaks/pork chops, and lunch meats, reflecting the changes in regulation of nitrate as a meat additive (51). In contrast, nitrate concentrations in bacon and breakfast sausage measured in 2004 were somewhat higher than the older published values. The processed meat nitrate and nitrite intakes estimated from literature values and from measured sources were highly correlated; as a result, these 2 approaches to exposure estimation did not result in very large differences in exposure classification.

The gender difference we observed was not statistically significant, but it may be partially explained by differential dietary reporting errors between men and women. Studies have found that healthful attitudes and dietary habits were more strongly correlated with vegetable intake among women than among men (52, 53) and that women overreported intake of foods perceived as healthy (54, 55). Compared with men, women in our cohort reported less absolute meat intake. Misreporting of processed meat intake by women in our study would have led to exposure misclassification, resulting in an attenuated association. It is also plausible that the higher red meat intake in men compared with women results in increased endogenous *N*-nitrosation and an increased risk in men but not in women. In a previous analysis in this study

population (6), high red meat intake was positively associated with pancreatic cancer among men but not among women (HR = 1.42, 95% CI: 1.05, 1.91). However, in the current analysis, we did not identify a statistically significant interaction between red meat intake and nitrate or nitrite intake.

Strengths of this study include the use of a detailed questionnaire to assess nitrate and nitrite intake, as well as the wide range of reported intakes; the median intake of nitrate in the highest quintile was over 5 times that in the lowest quintile, and for nitrite, intake in the highest quintile was over 3 times that in the lowest quintile. Other strengths include the prospective nature of the study, the completeness of follow-up, the relatively large number of pancreatic cancer cases, and the ability to adjust for a large number of potentially confounding variables. Limitations include the possibility that dietary intake based on food frequency questionnaires is affected by measurement error, which, if nondifferential, could attenuate associations. Furthermore, recall of diet during adolescence may be associated with measurement error because of the length of time associated with the recall. There is also the possibility that something else besides nitrate and nitrite in foods that was not measured could be associated with pancreatic cancer.

In sum, we found a nonsignificantly increased risk of pancreatic cancer in men with higher nitrate and nitrite intakes from processed meats. These results were also observed in an analysis of dietary intake during adolescence. Because screening for and early detection of pancreatic cancer are not feasible at this time, there is no effective treatment for this formidable disease, aside from surgery for a small minority of patients; therefore, the identification of preventable exposures such as dietary factors is an important area of investigation. However, our results provide only very modest evidence of a potential role of nitrate and nitrite in pancreatic cancer risk among men.

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